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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/583,469	06/19/2006	Motoyuki Tanaka	Q95536	2589

23373 7590 12/04/2009

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EXAMINER	
HAVLIN, ROBERT H	

ART UNIT	PAPER NUMBER
1626	

NOTIFICATION DATE	DELIVERY MODE
12/04/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/583,469	TANAKA ET AL.	
	Examiner	Art Unit	
	ROBERT HAVLIN	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 September 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5-7,9-13,15,16 and 18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5-7,9-13,15,16 and 18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

RCE: A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/11/09 has been entered.

Status of the claims: Claims 1, 2, 5-7, 9-13, 15,16, and 18 are currently pending.

Priority: This application is a 371 of PCT/JP04/19456 (12/17/2004) and claims foreign priority to JAPAN P.2003-422431 (12/19/2003) and JAPAN P.2004-101378 (03/30/2004).

Declaration: The declaration of Masahiko Terakado under 37 CFR 1.132 filed 8/11/09 is insufficient to overcome the rejection of claim 16 based upon 35 USC 112 as set forth in the last Office action because: the data presented in the declaration is not commensurate in scope with the claims and the unpredictability in the art, as detailed in the prior office action, is such that one of ordinary skill in the art would not have an expectation that the results described for the 12 compounds would equally apply to the billions of species within the genus. The conclusion of unpredictability in the art is also supported by the variations in the IC50 data presented in the declaration because the values vary by more than an order of magnitude even with only minor structural variations.

Claim Rejections - 35 USC § 112

1. Claims 1-10, 12-16, and 18 were rejected under 35 USC 112 1st paragraph as failing to comply with the written description requirement. As noted in the advisory action, this rejection is **withdrawn**.

Claim Rejections - 35 USC § 112 - Enablement

2. Claim 16 was rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for prevention and/or treatment of the claimed disorders with the full scope of compounds encompassed by claim 1.

Applicant has submitted the Terakado declaration disclosing 12 compounds with IC50 in vitro data. As discussed above, this scope is not commensurate with the claim scope. Regarding applicant's attempt to rebut the enablement rejection, MPEP 2164.05 provides (emphasis added):

> Once the examiner has weighed all the evidence and established a reasonable basis to question the enablement provided for the claimed invention, the burden falls on applicant to present persuasive arguments, supported by suitable proofs where necessary, that one skilled in the art would be able to make and use the claimed invention using the application as a guide. In re Brandstadter, 484 F.2d 1395, 1406-07, 179 USPQ 286, 294 (CCPA 1973). The evidence provided by applicant need not be conclusive but merely convincing to one skilled in the art.
>
> Applicant may submit factual affidavits under 37 CFR 1.132 or cite references to show what one skilled in the art knew at the time of filing the application. A declaration or affidavit is, itself, evidence that must be considered. The weight to give a declaration or affidavit will depend upon the amount of factual evidence the declaration or affidavit contains to support the conclusion of enablement. In re Buchner, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991) ("**expert's opinion on the ultimate legal conclusion must be supported by something more than a conclusory statement**"); cf. In re Alton, 76 F.3d 1168, 1174, 37 USPQ2d 1578, 1583 (Fed. Cir. 1996) (declarations relating to the written description requirement should have been considered).
>
> Applicant should be encouraged to provide any evidence to demonstrate that the disclosure enables the claimed invention. In chemical and biotechnical applications, evidence actually submitted to the FDA to obtain approval for clinical trials may be submitted. However, considerations made by the FDA for approving clinical trials are different from those made by the PTO in determining whether a claim is enabled. See Scott v. Finney, 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 (Fed. Cir. 1994) ("Testing for full safety and effectiveness of a prosthetic device is more properly left to the [FDA]."). Once that evidence is submitted, it must be weighed with all other evidence according to the standards set forth above so as to reach a determination as to whether the disclosure enables the claimed invention.

> To overcome a prima facie case of lack of enablement, applicant must demonstrate by argument and/or evidence that **the disclosure, as filed, would have enabled the claimed invention for one skilled in the art at the time of filing**. This does not preclude applicant from providing a declaration after the filing date which demonstrates that the claimed invention works. However, **the examiner should carefully compare the steps, materials, and conditions used in the experiments of the declaration with those disclosed in the application to make sure that they are commensurate in scope**; i.e., that the experiments used the guidance in the specification as filed and what was well known to one of skill in the art. **Such a showing also must be commensurate with the scope of the claimed invention, i.e., must bear a reasonable correlation to the scope of the claimed invention**.
>
> The examiner must then weigh all the evidence before him or her, including the specification and any new evidence supplied by applicant with the evidence and/or sound scientific reasoning previously presented in the rejection and decide whether the claimed invention is enabled. The examiner should never make the determination based on personal opinion. The determination should always be based on the weight of all the evidence.

The evidence provided by applicant does not demonstrate that one of skill in the art would be able to practice the full scope of the invention based on the disclosure because of the unpredictability in the art. Specifically, one of skill in the art would need to synthesize and screen all of the more than one billion species to identify those that are actually active. Heasley et al. demonstrates that small changes in a compound's structure can have dramatic effects in activity in the same way as was shown by Kubinyi. For example, tables I and II of Heasley show that the certain substitutions on the phenyl ring of LPA antagonists, which are analogs to the claimed compounds, render the compound inactive.

Although applicant argues "the present sepcification provides in vivo data showing that a compound within the scope of the present claims has an effect on urethral pressure, which can be reasonably correlated to the claimed method of treatment and other compounds within the scope of the present claims," this argument is not persuasive because the prior art shows that analogous compounds with minor variations in structure have levels of activity below what would be useful. Therefore, the

unpredictability in the art combined with the disclosure of a single compound showing in vitro activity only allows the conclusion that the full scope as claimed is not enabled. Accordingly, the rejection is **maintained**.

NEW CLAIM REJECTIONS

Claim Rejections - 35 USC § 102

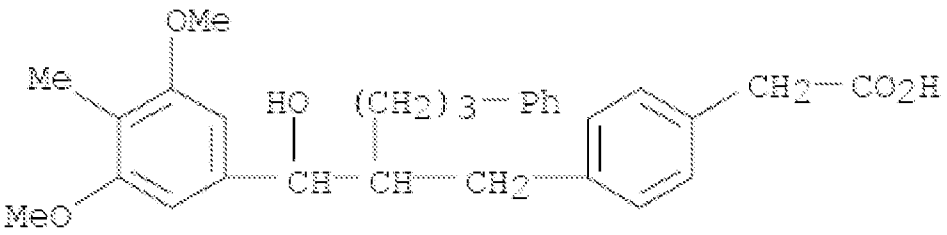
3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

4. Claims 1, 2, 6, 7, 9, 12, 13, 15, and 16 are rejected under 35 U.S.C. 102(e) as being anticipated by US 2006/0148830.

The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Example 31 teaches the following compound which anticipates the claims:

5. 

.

6. Applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1, 2, 5-7, 9, 10, 12, 13, 15, and 18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the compounds identified as having inhibitory effect with experimental data, does not reasonably provide enablement for the asserted utility of the entirety of the claim scope. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Particularly relevant to the instant case is the issue as to whether the specification provides embodiments allowing use of the claimed invention without requiring undue experimentation by one of ordinary skill in view of the highly unpredictable nature of inhibiting enzymes.

> "[An inventor] must not be permitted to achieve . . . dominance by claims which are insufficiently supported and hence not in compliance with the first paragraph

> of 35 U.S.C. 112. That paragraph requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. In cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved." *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

Accordingly, the critical element here how broad the claims are compared to the level of unpredictability in the art.

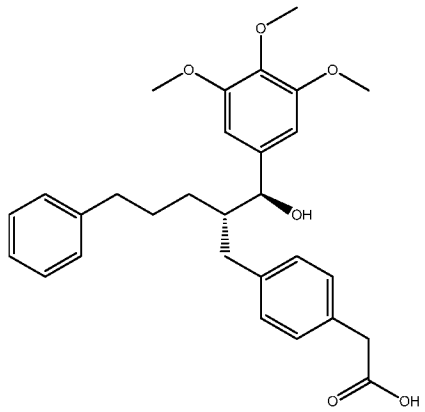
The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the specification coupled with information known in the art without undue experimentation (*United States v. Telectronics*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is needed is not based upon a single factor but rather is a conclusion reached by weighing many factors. These factors were outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Int. 1986) and again in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988) and include the following:

Nature of Invention. The nature of the invention involves pharmaceutical compounds for affecting enzymes.

Scope of the Invention. The scope of the invention are for a genus of compounds with in excess of billions of species.

State of the Art and Level of Skill in the Art. Although the level of skill in the art is very high, inhibiting enzymes is a very unpredictable art. Kubinyi (3D QSAR in Drug Design: Ligand-Protein Interactions and Molecular Similarity, Vol 2-3, Springer, 1998, 800 pages) teaches that very slight perturbations in the structure of an inhibitor (such as the addition of a methyl group or inversion of a chiral center, see p. 243) can have radical effects on the binding of an inhibitor. Similarly, Heasley et al. (Bioorganic & Medicinal Chemistry Letters 14 (2004) 2735–2740) teaches how small structural changes in LPA antagonists can have radical effects on the activity of a compound.

Number of Working Examples and Guidance Provided by Applicant. The applicant provided in vitro IC50 data for a single compound with the following structure:



(4- { (2S)-2-[(S)-hydroxy(3,4,5-trimethoxyphenyl)methyl]-5-phenylpentyl } phenyl)acetic acid. See page 137 of the specification.

Unpredictability of the Art and Amount of Experimentation. The art of using pharmaceuticals to affect enzymes is highly unpredictable as described by Kubinyi and Heasley. In nearly every case, the skilled artisan could not predict *a priori* whether a given pharmaceutical would affect an enzyme. When small variations in structure such as the addition of a methyl group has radical effects on the binding of an inhibitor, without specific guidance or correlations indicating how the structure of species affects its ability to inhibit an enzyme the scope of enablement is constrained to compounds showing substantial similarity to those actually demonstrated to be useful. Furthermore, there would be a huge amount of undue experimentation required in order to synthesize and screen the billions of compounds within the claimed scope.

Considering the above factors, the claims are not enabled for the full scope of the compounds claimed. The examiner recommends either amending the claim scope to only those compounds closely resembling the compounds actually tested and disclosed in the specification or provide additional data and/or structural correlations to guide one of ordinary skill in the art to compounds possessing the asserted utility.

9. Claims 1, 2, 5-7, 9-13, 15, 16, and 18 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for "solvates thereof." The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Nature of Invention. The nature of the invention involves pharmaceutical compounds including solvates forms unknown.

Scope of the Invention. The scope of the invention are for a genus of compounds of having in excess of billions of species and solvates thereof.

State of the Art and Level of Skill in the Art. The formation of solvates is highly unpredictable due to the complex interplay between the solvent and the structural elements of the compound that is not well understood (see Byrn et al., Pharm. Res., v. 12, n. 7, p945-54, 1995). One of ordinary skill in the art could not predict whether a particular solvate would form.

Number of Working Examples and Guidance Provided by Applicant. The applicant provides no working examples or guidance regarding solvates.

Unpredictability of the Art and Amount of Experimentation. The formation of solvates is highly unpredictable and one of ordinary skill in the art could not predict whether a particular solvate would form, to determine this requires trial and error experimentation that would be an undue burden. Furthermore, there would be a huge amount of undue experimentation required in order to synthesize and screen the billions of compounds within the claimed scope for any possible solvate.

Considering the above factors, the claims are not enabled for solvates of the compounds claimed.

Conclusion

The claims are not in condition for allowance.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ROBERT HAVLIN whose telephone number is (571)272-9066. The examiner can normally be reached on Mon. - Fri., 7:30am-5pm EST.

If attempts to reach the examiner by telephone are unsuccessful the examiner's supervisor, Joe McKane can be reached at (571) 272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Robert Havlin/
Examiner, Art Unit 1626

/Kamal A Saeed, Ph.D./
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